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Efficacy and safety of current therapeutic options for COVID-19 - lessons to be learnt from SARS and MERS epidemic: A systematic review and meta-analysis



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ABSTRACT

The rapidly progressing of coronavirus disease 2019 (COVID-19) pandemic has become a global concern. This meta-analysis aimed at evaluating the efficacy and safety of current option of therapies for severe acute respiratory syndrome (SARS), Middle Eastern respiratory syndrome (MERS) besides COVID-19, in an attempt to identify promising therapy for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients.

We searched PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and WANFANG DATA for randomized controlled trials (RCTs), prospective cohort, and retrospective cohort studies that evaluated therapies (hydroxychloroquine, lopinavir/ritonavir-based therapy, and ribavirin-based therapy, etc.) for SARS, MERS, and COVID-19. The primary outcomes were mortality, virological eradication and clinical improvement, and secondary outcomes were improvement of symptoms and chest radiography results, incidence of acute respiratory disease syndrome (ARDS), utilization of mechanical ventilation, and adverse events (AEs). Summary relative risks (RRs) and 95% confidence intervals (CIs) were calculated using random-effects models, and the quality of evidence was appraised using GRADEpro.

Eighteen articles (5 RCTs, 2 prospective cohort studies, and 11 retrospective cohort studies) involving 4,941 patients were included. Compared with control treatment, anti-coronavirus interventions significantly reduced mortality (RR 0.65, 95% CI 0.44-0.96; $I^2 = 81.3\%$), remarkably ameliorate clinical improvement (RR 1.52, 95% CI 1.05-2.19) and radiographical improvement (RR 1.62, 95% CI 1.11-2.36, $I^2 = 11.0\%$), without manifesting clear effect on virological eradication, incidence of ARDS, intubation, and AEs. Subgroup analyses demonstrated that the combination of ribavirin and corticosteroids remarkably decreased mortality (RR 0.43, 95% CI 0.27-0.68). The lopinavir/ritonavir-based combination showed superior virological eradication and radiographical improvement with reduced rate of ARDS. Likewise, hydroxychloroquine improved radiographical result. For safety, ribavirin could induce more bradycardia, anemia and transaminitis. Meanwhile, hydroxychloroquine could increase AEs rate especially diarrhea. Overall, the quality of evidence on most outcomes were very low.

In conclusion, although we could not draw a clear conclusion for the recommendation of potential therapies for COVID-19 considering the very low quality of evidence and wide heterogeneity of interventions and indications, our results may help clinicians to comprehensively understand the advantages and drawbacks of each anti-coronavirus agents on efficacy and safety profiles. Lopinavir/ritonavir combinations might observe better virological eradication capability than other anti-coronavirus agents. Conversely, ribavirin might cause more safety concerns especially bradycardia. Thus, large RCTs objectively assessing the efficacy of antiviral therapies for SARS-CoV-2 infections should be conducted with high priority.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a novel viral respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. The first report took place in China in 2019 and subsequently spread across the globe rapidly. As of 14 April 2020, a total of 1,844,863 confirmed infections have been reported with 117,021 deaths [3]. Upon the emerging COVID-19, there is no known approved, specific, effective antiviral treatment to treat this fatal disease [4]. Therefore, it is of utmost urgency to identify potential therapies for SARS-CoV-2 infected patients [5].

As the COVID-19 resemble severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS) phylogenetically and symptomatically, a variety of agents have been tried according to the clinical experience from SARS and MERS [6,7]. The broad-spectrum antiviral agent ribavirin [8], protease inhibitor lopinavir and ritonavir [9,10] and immune up-regulator interferon [11,12] were most commonly used. In addition, *in vitro* or *in vivo* studies have suggested that chloroquine and hydroxychloroquine [13,14], remdesivir [15] and arbidol [16] are effective in inhibiting viral replication in SARS-associated coronavirus (CoV), MERS-CoV and SARS-CoV-2 infections [17]. However, the efficacy and safety of these treatments for COVID-19 remains unclear [4].

Few systematic reviews have previously summarized clinical trials of potential therapeutic agents for SARS, MERS or COVID-19, resulting in inconclusive outcomes [4,18–21]. Herein, we conduct this review to identify the efficacy and safety of current option of therapies for SARS, MERS besides COVID-19, in an attempt to identify promising therapy for SARS-CoV-2 infected patients.

2. Methods

The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and previously published protocol (PROSPERO: CRD42020168639).

2.1. Literature searches

A comprehensive searching of PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and WANFANG DATA was performed from inception to April 14th, 2020 without language restriction. Unpublished trials were also identified from clinical trial registry platforms (<http://clinicaltrials.gov/> and <http://www.chictr.org.cn/>). Preprint articles were also retrieved from the websites MedRxiv (<https://www.medrxiv.org>) and BioRxiv (<https://www.biorxiv.org>). Manual search was conducted by screening the reference lists of inclusive studies. The search strategy consisting of patient relevant terms (COVID-19, Middle East respiratory syndrome, severe acute respiratory syndrome, etc.) and intervention relevant terms (lopinavir, ritonavir, chloroquine, hydroxychloroquine, interferon, ribavirin, remdesivir, arbidol, etc.) was applied both in Medical Subject Headings (MeSH) and free text. The comprehensive search syntax was available in Supplemental Table 1.

2.2. Study selection and outcomes

Two authors (Z. Z. and H.Z.) independently screened the titles, abstracts and full-text of retrieved articles to identify their eligibility (Fig. 1). The studies were considered for inclusion if they were randomized controlled trials (RCTs), prospective cohort, or retrospective cohort studies; performed among adult patients with COVID-19 or MERS or SARS; evaluated the efficacy and safety of anti-coronavirus agents. Furthermore, the studies were considered to be excluded if they lacked a control group or target quantitative outcomes; were *in vitro* or

in vivo studies. Disagreements will be resolved by discussions with the corresponding author (Z. G.). The primary outcomes of this study included mortality, virological eradication, and clinical improvement. The secondary outcomes included improvement of symptoms, time to become afebrile, improvement of chest radiography results, utilization of mechanical ventilation, intensive care unit admission, and adverse events (AEs).

2.3. Data extraction and quality assessment

Data extraction was independently conducted by two authors (H. Z. and Z. Z.) using a standardized data collection form, which included study characteristics (author, year of publication, region, study design, sample size), population characteristics (age, gender, indication), intervention characteristics (anti-coronavirus agents, dosage, duration, concomitant therapy), and outcomes (mortality, viral eradication, clinical outcomes, and AEs). The risk of bias of inclusive RCTs were assessed in accordance with the Cochrane Collaboration Risk of Bias Tool [22]. The methodological quality assessment of prospective cohort and retrospective cohort studies were performed using the New-castle Ottawa Scale (NOS) [23]. The risk of bias of individual study was rated as low, moderate, or high. The quality of evidence was assessed with the GRADEpro software and were graded as high, moderate, low, and very low [24].

2.4. Data synthesis and statistical analysis

Dichotomous data was shown as relative risks (RR) with 95% confidence intervals (CIs) and continuous variables were calculated as weight mean difference (WMD) with associated 95% CIs using random-effects model, with a $I^2 > 50\%$ representing notable heterogeneity [25]. Subgroup analysis for treatments including hydroxychloroquine, lopinavir/ritonavir alone or combination, ribavirin alone or combination, arbidol and interferon were performed. To detect the robustness of the results, sensitivity analysis was conducted by sequential elimination of each study from the pool. Potential publication bias was assessed using visual inspection of funnel plots when the number of included studies was more than ten. Statistics were performed using STATA software (version13, Statacorp, College Station, Texas, USA), with $P < 0.05$ indicating a statistically significant difference.

3. Results

The present searches totally identified 5,192 citations and excluded 5,105 publications after cautious screening of titles and abstracts. Of the 87 potential studies, full-text were assessed for eligibility, 69 were excluded because they were reviews, did not contain eligible comparators, did not report outcomes of interest, were case series or others (Fig. 1). Finally, 18 articles [10,12,26–41] with 4,941 patients met the inclusion criteria and were retrieved for quantitative synthesis (Table 1).

3.1. Description of studies

There were 5 RCTs [28,37,38,40,41] and 2 prospective studies [12,32], whilst the remaining 11 trials were retrospective studies [10,26,27,29–31,33–36,39]. Thirteen studies were conducted in China [10,27,28,30,31,33–38,40,41], 3 in Canada [12,26,31], 2 in Saudi Arabia [29,39], and 1 in France [32].

There were 7 studies involving patients with COVID-19 [27,28,32,36–38,40], 9 studies involving patients with SARS [10,12,26,30,31,33–35,41], and 2 studies involving patients with MERS [29,39]. The interventions included arbidol (1 study) [36], arbidol and lopinavir/ritonavir (1 study) [37], hydroxychloroquine (4 studies) [28,32,37,40], interferon and corticosteroid (2 studies) [12,30], lopinavir/ritonavir (2 studies) [36,38], lopinavir/ritonavir

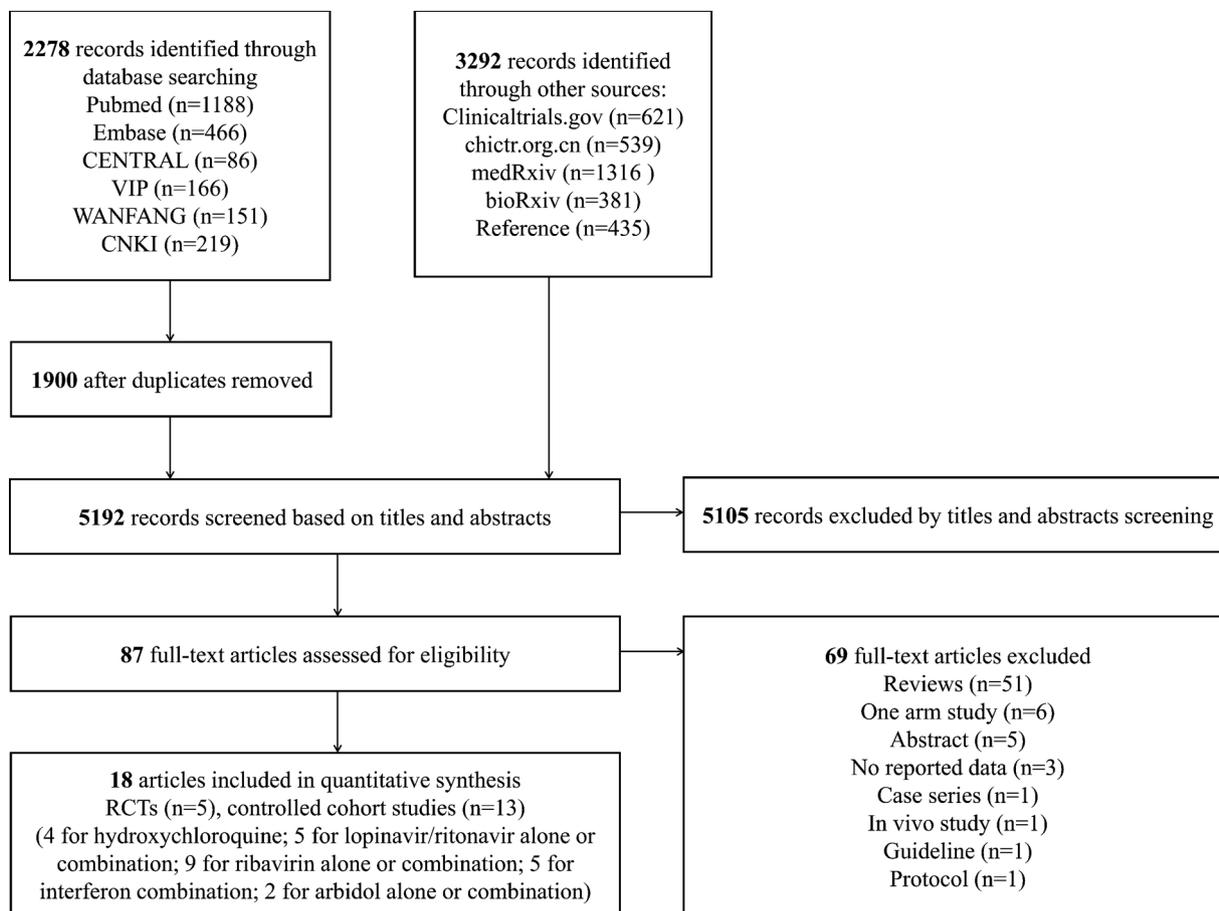


Fig. 1. Flow diagram of assessed and included studies. CENTRAL: Cochrane Central Register of Controlled Trials; CNKI: China National Knowledge Infrastructure; RCTs: Randomized controlled trials; VIP: China Science and Technology Journal Database.

plus ribavirin and corticosteroids (2 studies) [10,35], ribavirin (4 studies) [26,31,33,41], ribavirin and interferon (3 studies) [29,34,39], ribavirin and corticosteroids (1 study) [31] (Table 1).

The primary outcomes were mortality reported in 10 studies (4,282 patients) [10,12,26,29,31,34,35,38,39,41], virological clearance reported in 7 studies (663 patients) [27,32,35–38,40], clinical improvement reported in 1 study (199 patients) [38]. The secondary outcomes were radiographical improvement reported in 2 studies (95 patients) [27,28], acute respiratory disease syndrome (ARDS) reported in 2 studies (346 patients) [35,38], intubation reported in 5 studies (1,494 patients) [10,12,26,29,41], and adverse events (AEs) reported in 4 studies (436 patients) [28,37,38,40], leukopenia reported in 2 studies (281 patients) [30,38], anemia reported in 4 studies (723 patients) [26,34,37,38], thrombocytopenia reported in 2 studies (387 patients) [34,38], transaminitis reported in 4 studies (633 patients) [26,34,37,38], elevated total bilirubin reported in 3 studies (330 patients) [27,34,38], elevated creatinine reported in 3 studies (324 patients) [36–38], bradycardia reported in 2 studies (487 patients) [26,33], and diarrhea reported in 5 studies (708 patients) [35–38,40].

3.2. Methodological quality of included studies

Considering RCTs, the information of randomization was unclear in 2 studies [37,41], while the concealing of allocation was absent or unclear in 3 studies [37,40,41]. Moreover, blinding of participants and the outcome assessors were absent or unclear in 4 studies [37,38,40,41] (Supplementary Table S2). Therefore, we decided to identify these 4 studies with risk of bias. In terms of observational studies, the NOS

scores were 6–9, indicating most of the studies were of low risk of bias (Supplementary Table S3).

3.3. Outcomes

3.3.1. Mortality

We performed a meta-analysis of the 10 studies (4,282 patients) demonstrating data on mortality when the indication was not considered [10,12,26,29,31,34,35,38,39,41]. Compared with comparators, interventions could notably reduce mortality (RR 0.65, 95% CI 0.44–0.96; $I^2 = 81.3\%$). In subgroup analysis, the combination of ribavirin and corticosteroids remarkably decreased mortality (RR 0.43, 95% CI 0.27–0.68). Besides, lopinavir/ritonavir, ribavirin and interferon, ribavirin, the combination of lopinavir/ritonavir, ribavirin and corticosteroids, showed tendency of lower mortality. On the contrary, the combination of interferon and corticosteroid demonstrated higher mortality tendency with no significant difference (Fig. 2 and Supplementary Fig. 1).

3.3.2. Virological response

Seven studies (663 patients) documented data on virological eradication when the indication was not taken into consideration [27,32,35–38,40]. The pooled result showed that the virological eradication ability of interventions were equal to that of comparator group (RR 1.33, 95% CI 0.97–1.81, $I^2 = 89.8\%$). In subgroup analysis, the combination of lopinavir/ritonavir and arbidol, and the combination of lopinavir/ritonavir, ribavirin and corticosteroids appeared to show a superior ability in virological eradication, generating RR of 1.77 (95% CI 1.11–

Table 1
Summary of demographic and clinical characteristics of included studies^a.

Study	Region	Indications	No. of patients		Age	Gender (male %)		Intervention	Control	Primary outcomes	Secondary outcomes
			I/C	I/C		I/C	I/C				
Randomized controlled trial Cao et al (2020)	China	COVID-19	99/100	58/58	61.6/59.0	Lopinavir/ritonavir (400 mg/100 mg) po q12 h × 14 days		Standard care	The lopinavir/ritonavir therapy showed higher percentage of clinical improvement and numerically lower mortality compared with standard care, while the viral RNA loads over time were similar in both groups.	The lopinavir/ritonavir therapy was associated with shorter intensive care unit stay, more gastrointestinal adverse events and less serious adverse events. There was no difference in time to clinical improvement, time from randomization to death, duration of oxygen therapy, and hospital length of stay.	
						31/31	44.1/45.2				45.2/48.4
Chen et al (2020)-1	China	COVID-19	15/15	50.5/46.7	60/80	Hydroxychloroquine sulfate tablets 200 mg bid po × 5 days		Standard care	Hydroxychloroquine showed no difference in negative conversion rate of coronavirus RNA test compared with control group. Hydroxychloroquine plus standard care showed comparable 28-day negative conversion rate.	Hydroxychloroquine observed no difference in time course of defervescence. The adverse effects were similar between groups. Symptoms alleviation rate were similar in two groups. Hydroxychloroquine reduced CRP and lymphopenia more rapidly. Hydroxychloroquine increased adverse events than standard care group.	
Chen et al (2020)-2	China	COVID-19	75/75	48.0/44.1	56.0/53.3	Hydroxychloroquine: Loading dose: 1200 mg qd × 3 days Maintenance dose: 800 mg qd × 2-3 weeks + Standard care		Standard care	Hydroxychloroquine plus standard care showed comparable 28-day negative conversion rate.	Hydroxychloroquine observed no difference in time course of defervescence. The adverse effects were similar between groups. Symptoms alleviation rate were similar in two groups. Hydroxychloroquine reduced CRP and lymphopenia more rapidly. Hydroxychloroquine increased adverse events than standard care group.	
Tang et al (2020)	China	COVID-19	40/30	33.6/32.4	38.5/36.7	Ribavirin 0.4-0.6 g qd iv + Gefoprazone/sulbactam 2 g bid iv		Fluoroquinolone + Azithromycin 0.4 g qd iv + Recombinant interferon-α 3 million U qd im	The death rates were equal in two groups.	Two groups had similar cases requiring mechanical ventilation.	
Prospective study Gautret et al (2020)	France	COVID-19	20/16	51.2/37.3	45.0/37.5	Hydroxychloroquine 200 mg po tid × 10 days ± Azithromycin: day 1: 500 mg; day 2-5: 250 mg qd		Supportive treatment	Hydroxychloroquine with or without azithromycin was associated with faster elimination of virus compared to controls. Azithromycin could facilitate the viral clearance effect of hydroxychloroquine.	NA	

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Table 1 (continued)

Study	Region	Indications	No. of patients	Age	Gender (male %)	Intervention	Control	Primary outcomes	Secondary outcomes
Loutfy et al (2003)	Canada	SARS	9/13	48/42	33.3/23.1 I/C	Interferon alfacon-1: 9-15 µg ih qd × 10 days + Corticosteroid: Prednisone 50 mg po bid, or methylprednisolone 40 mg iv q12 h	Corticosteroids alone	In interferon alfacon-1 and corticosteroids group, less patients died than corticosteroids alone group.	Interferon alfacon-1 and corticosteroids treatment could result in less intensive care unit admission, lower rate of intubation and mechanical ventilation requirement. This combination also showed higher oxygen saturation, faster resolution of radiographic lung abnormalities, and reduced levels of creatine kinase.
Retrospective cohort study									
Chen et al (2020)-3	China	COVID-19	Lopinavir /ritonavir: 52; Arbidol: 34; Control: 48	Lopinavir /ritonavir: 47; Arbidol: 44; Control: 55	Lopinavir /ritonavir: 51.9; Arbidol: 52.9; Arbidol: 50.0	Lopinavir/ritonavir (400 mg/100 mg) po q12 h × 5 days or Arbidol 0.2 g po tid × 5 days + Interferon-α2b spray and supportive treatment	Interferon-α2b spray and supportive treatment	Lopinavir/ritonavir or arbidol showed no difference in negative conversion rate of coronavirus RNA test compared with control group.	Lopinavir/ritonavir or arbidol observed no difference in time course of defervescence and resolution of radiographic lung abnormalities. The adverse effects were similar between groups. Combination therapy group exhibited a significantly improved chest CT scans in 7-day. Adverse effects including elevated levels of bilirubin, gastrointestinal upset in both groups.
Deng et al (2020)	China	COVID-19	16/17	41.8/47.25	43.8/58.8	Arbidol 200 mg po q8h + Lopinavir/ritonavir (400 mg/100 mg) po q12 h × 5-21 days	Lopinavir / ritonavir (400 mg/100 mg) po q12 h × 5-21 days	Arbidol and lopinavir/ritonavir group showed a significant elevated negative conversion rate of coronavirus' test in 7-day and 14-day, compared with lopinavir/ritonavir monotherapy group.	There was no difference in terms of duration of invasive mechanical ventilation and hospital length of stay between ribavirin and interferon group and control group. ICU length of stay was longer in ribavirin and interferon group.
Arabi et al (2019)	Saudi Arabia	MERS	144/205	57.5/58	70.1/68.3	Ribavirin and interferon	Without ribavirin and interferon	Ribavirin and interferon group showed no difference in 90-day mortality and MERS-CoV RNA clearance with control group.	Two groups observed similar utilization rate of mechanical ventilation, extracorporeal membrane oxygenation, and renal replacement therapy. The combination showed significant falls in hemoglobin, but no other significant adverse effects.
Omrani et al (2014)	Saudi Arabia	MERS	20/24	67.4/64	80.0/66.7	Ribavirin: Loading dose: 2000 mg po; maintenance dose: adjusted according to creatinine clearance × 8-10 days + Interferon-α2a: 180 µg ih qw × 2 weeks	Without ribavirin and interferon	Ribavirin and interferon group observed significantly improved survival at 14 days, but not at 28 days.	NA
Lau et al (2009)-A	Hong Kong, China	SARS	202/751	NA	NA	Ribavirin	None	The combination of ribavirin and corticosteroids had no benefit in terms of survival.	NA
Lau et al (2009)-B	Hong Kong, China	SARS	739/51	NA	NA	Ribavirin and corticosteroids	Corticosteroids only		
Lau et al (2009)-C	Canada	SARS	107/45	NA	NA	Ribavirin	None		

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Table 1 (continued)

Study	Region	Indications	No. of patients	Age	Gender (male %)	Intervention	Control	Primary outcomes	Secondary outcomes
Muller et al (2007)	Canada	SARS	183/123 I/C	44/45 I/C	39.9/33.3 I/C	Ribavirin: Very high dose: Loading dose: 2000 mg iv; maintenance dose: 1000 mg iv q8h × 4 days, 500 mg q6h × 3 days High dose: NA	Without ribavirin	Patients treated with and without ribavirin observed similar mortality.	Two groups observed similar utilization rate of mechanical ventilation. Ribavirin was strongly associated with anemia, hypomagnesemia, and bradycardia.
Li et al (2005)	China	SARS	41/46	29.3/26.7	19.5/17.4	Interferon-α 1 million units ih / im qd × 6-10 days + Methylprednisolone 80-160 mg/d	Methylprednisolone alone	NA	The defervescence rates were indistinguishable between groups. The combination of interferon-α and methylprednisolone was associated with shorter hospital length of stay, faster resolution of radiographic lung abnormalities, less need of corticosteroids. The percentages of leukopenia were similar between groups.
Fu et al (2004)	China	SARS	135/46	32/36	41.5/50.0	Ribavirin: 200 mg po q8h > 5 days, or 500 mg iv q8h > 5 days	Supportive treatment	NA	Ribavirin was associated with bradycardia.
Chu et al (2004)	China	SARS	41/111	39.4/42.1	24.4/43.2	Lopinavir/ritonavir (400 mg/100 mg) po q12 h × 14 days + Ribavirin: Loading dose: 4 g po, maintenance dose: 1.2 g po q8h, or 8 mg/kg iv q8h × 14 days + Corticosteroid: Reducing regimen	Ribavirin: Loading dose: 4 g po, maintenance dose: 1.2 g po q8h, or 8 mg/kg iv q8h × 14 days + Corticosteroid: Reducing regimen	The lopinavir/ritonavir treatment group showed reduced frequencies of recurrent fever, worsening of the chest radiography and diarrhea. Mild adverse reaction rates were similar in both groups.	
Fu et al (2003)	China	SARS	Ribavirin + interferon: 132; Ribavirin: 61; Interferon: 7	NA	NA	Corticosteroid: Reducing regimen Ribavirin: 200 mg po q8h × approx. 10 days + Interferon: 1 million units im qd × approx. 10 days	Ribavirin: Loading dose: 4 g po, maintenance dose: 1.2 g po q8h, or 8 mg/kg iv q8h × 14 days + Corticosteroid: Reducing regimen	The mortality was notably lower in combination group and interferon alone group compared to ribavirin group.	The combination of ribavirin and interferon was associated with delayed reduction of T cells. The interferon alone had less effects on blood cell counts, kidney and liver function.
Chan et al (2003)-A	China	SARS	44/634	NA	27.3/NA	Lopinavir/ritonavir as initial treatment: 400 mg/100 mg po q12 h × 10 to 14 days + Ribavirin: Loading dose: 2.4 g po, maintenance dose: 1.2 g po q8h, or 8 mg/kg iv q8h × 10 to 14 days + Corticosteroid: Tailing regimen × 21 days	Ribavirin: Loading dose: 2.4 g po, maintenance dose: 1.2 g po q8h, or 8 mg/kg iv q8h × 10 to 14 days + Corticosteroid: 14 days + Corticosteroid: Tailing regimen × 21 days	The lopinavir/ritonavir as initial therapy was associated with lower mortality compared with matched cohorts. The Lopinavir/ritonavir as rescue therapy observed no difference in mortality, compared with matched cohorts.	The Lopinavir/ritonavir as initial therapy was associated with lower rate of incubation and use of corticosteroids at a reduced dose compared with matched cohorts. The lopinavir/ritonavir as rescue therapy observed no difference in rates of intubation and oxygen desaturation compared with matched cohorts.
Chan et al (2003)-B	China	SARS	31/343	NA	41.9/NA	Lopinavir/ritonavir as rescue therapy: 400 mg/100 mg po q12 h × 10 to 14 days + Ribavirin: Loading dose: 2.4 g po, maintenance dose: 1.2 g po q8h, or 8 mg/kg iv q8h × 10 to 14 days + Corticosteroid: Tailing regimen × 21 days	Ribavirin: Loading dose: 2.4 g po, maintenance dose: 1.2 g po q8h, or 8 mg/kg iv q8h × 10 to 14 days + Corticosteroid: 14 days + Corticosteroid: Tailing regimen × 21 days		

^a C: Control group; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; I: intervention group; MERS: Middle Eastern respiratory syndrome; MERS-CoV: MERS-associated coronavirus; NA: Not available; RNA: Ribonucleic acid; RT-PCR: Reverse transcriptase polymerase chain reaction; SARS: Severe acute respiratory syndrome.

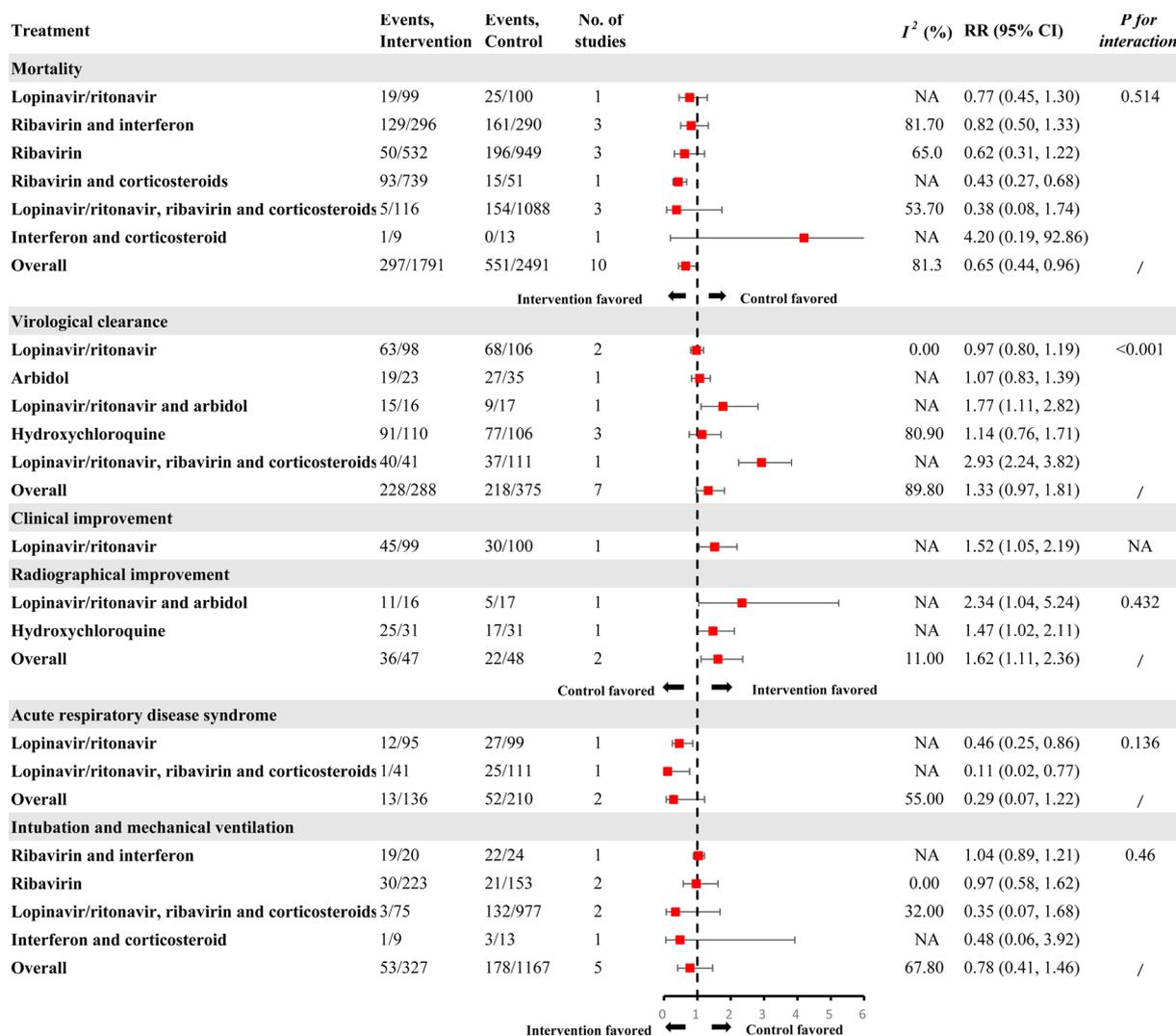


Fig. 2. Efficacy of anti-coronavirus interventions compared with control group. RR: Risk ratio; CI: Confidence interval.

2.82), RR of 2.93 (95% CI 2.24-3.82), respectively. Additionally, the value of *P* for interaction was less than 0.01, indicating a significant difference across treatments (Fig. 2 and Supplementary Fig. 2).

3.3.3. Clinical response

Only 1 study (199 patients) reported clinical improvement of interventions. It is documented that lopinavir/ritonavir could ameliorate clinical improvement significantly (RR 1.52, 95% CI 1.05-2.19) (Fig. 2 and Supplementary Fig. 3).

For improvement of symptoms, there was only 1 study (150 patients) reported that the hydroxychloroquine-treated group observed similar rate of symptoms alleviation with standard care group (59.9% vs 66.6%) [40].

There were 4 studies (313 patients) demonstrated time to become afebrile. The present of data were diversity, showing as mean ± SD or medium (range), thus we could not generate a meta-analysis of this outcome. In addition, the results were controversial. On one hand, one study reported hydroxychloroquine treatment significantly shortened fever recovery time than control group 2.2 ± 0.4 vs 3.2 ± 1.3 [28]. On the other hand, Chen et al showed hydroxychloroquine treatment observed no difference in time course to become afebrile, which is 1(0-2) vs 1(0-3) [37]. Another 2 studies also documented that the lopinavir/ritonavir, arbidol, and the combination of interferon and corticosteroids therapies had no effects on time course of defervescence compared to control therapy [30,36].

As for radiographical improvement, the meta-analysis of 2 studies generated a RR of 1.62 (95% CI 1.11-2.36, $I^2 = 11.0\%$), indicating a superior ability of interventions for radiographical improvement. In subgroup analysis, the combination of lopinavir/ritonavir and arbidol, and hydroxychloroquine both showed notable benefits in radiographical outcomes (Fig. 2 and Supplementary Fig. 4).

Two studies reported data on acute respiratory disease syndrome (ARDS). There was no significant difference between the intervention group and control group (RR 0.29, 95% CI 0.07-1.22; $I^2 = 55\%$), despite the lopinavir/ritonavir alone and the combination of lopinavir/ritonavir, ribavirin and corticosteroids both observed notably lower incidence of ARDS (RR 0.46, 95% CI 0.25-0.86, RR 0.11, 95% CI 0.02-0.77, respectively) (Fig. 2 and Supplementary Fig. 5).

In terms of intubation and mechanical ventilation, 5 studies (1,494 patients) reported this outcome. The integrated data demonstrated that the incidence of intubation or mechanical ventilation in intervention group was equal to that in control groups (RR 0.78, 95% CI 0.41-1.46; $I^2 = 67.8\%$). The subgroup analysis showed similar results (Fig. 2 and Supplementary Fig. 6).

3.3.4. Safety

There was no significant difference in total rate of AEs across the intervention and control groups (RR 1.74, 95% CI 0.72-4.18; $I^2 = 71.0\%$). As for subgroup analysis, hydroxychloroquine treatment induced more AEs (RR 2.75, 95%CI 1.42-5.33, $I^2 = 0\%$), especially the

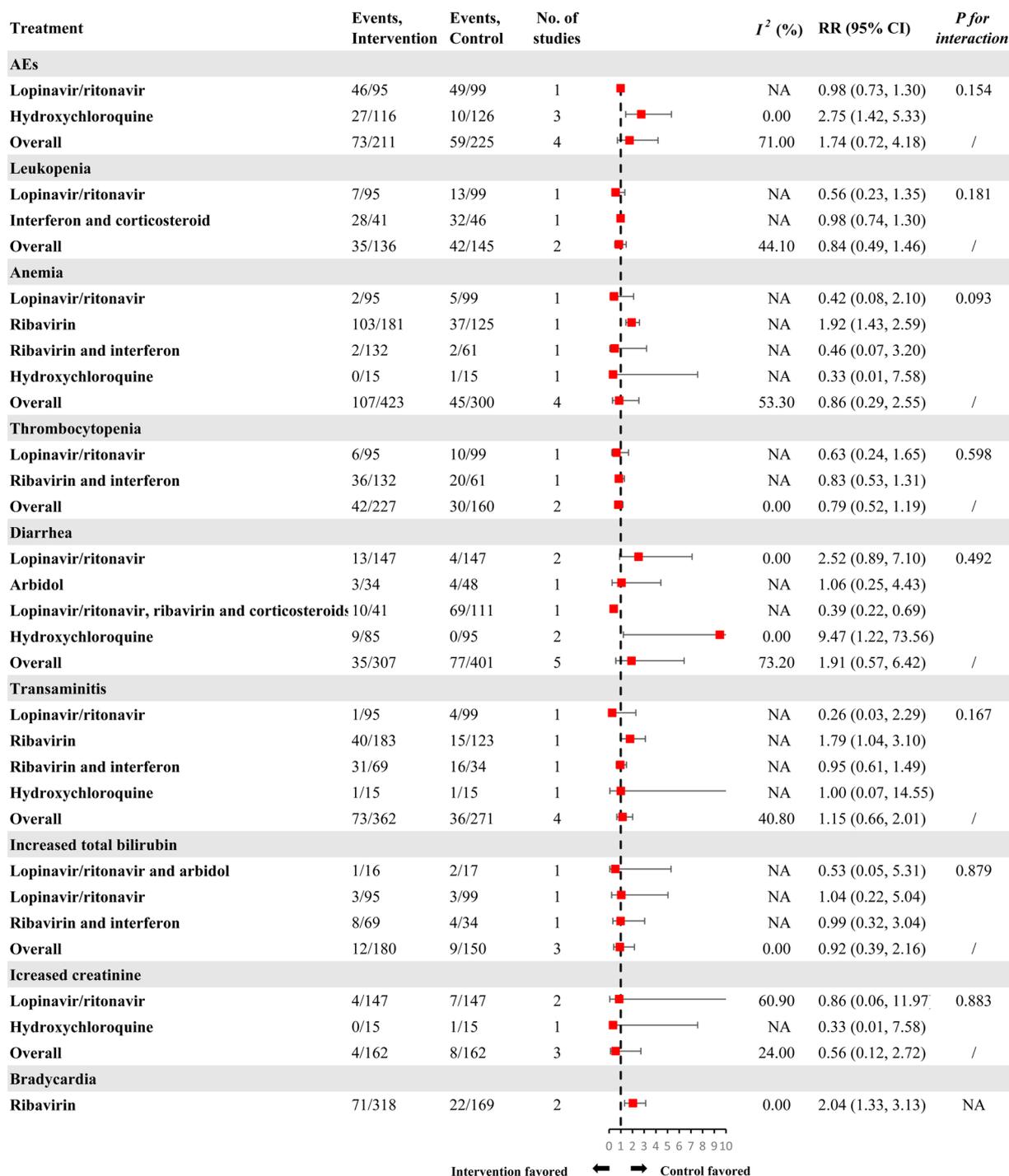


Fig. 3. Safety of anti-coronavirus interventions compared with control group. RR: Risk ratio; CI: Confidence interval; AEs: Adverse events.

diarrhea events (RR 9.47, 95%CI 1.22-73.56, $I^2 = 0\%$). It was reported that ribavirin could induce more bradycardia (RR 2.04, 95%CI 1.33-3.13), anemia (RR 1.92, 95%CI 1.43-2.59) and transaminitis (RR 1.79, 95%CI 1.04-3.10) compared with control group. Moreover, the combination of lopinavir/ritonavir, ribavirin and corticosteroids might reduce incidence of diarrhea compared with control group (RR 0.39, 95%CI 0.22-0.69) (Fig. 3 and Supplementary Figs. 7–15).

3.4. Sensitivity analyses and publication bias

Because of inadequate inclusive studies, we did not perform a sensitivity analysis to assess the influence of each included study. We did

not generate funnel plot to evaluate publication bias either with the same reason.

3.5. Effects of interventions

The quality of evidence is outlined in Table 2. The quality of findings relevant to mortality, virological clearance, radiographical improvement, prevalence of ARDS, intubation and mechanical ventilation were very low. In addition, the total AEs, leukopenia, anemia, thrombocytopenia, diarrhea, transaminitis, increased total bilirubin had very low quality of evidence as well. However, the outcome quality of clinical improvement and increased creatinine were low, while the

Table 2
The quality of evidence.

Outcomes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Mortality	RR 0.65 (0.44 to 0.96)	4282 (10 studies)	⊕⊕⊕⊕ very low ^{a,b}
Virological clearance	RR 1.33 (0.97 to 1.81)	663 (7 studies)	⊕⊕⊕⊕ very low ^{a,c,d}
Clinical improvement	RR 1.52 (1.05 to 2.19)	199 (1 study)	⊕⊕⊕⊕ low ^{a,c}
Radiographical improvement	RR 1.62 (1.11 to 2.36)	95 (2 studies)	⊕⊕⊕⊕ very low ^e
Acute respiratory disease syndrome	RR 0.29 (0.07 to 1.22)	346 (2 studies)	⊕⊕⊕⊕ very low ^c
Intubation and mechanical ventilation	RR 0.78 (0.41 to 1.46)	1494 (5 studies)	⊕⊕⊕⊕ very low ^{c,f,g}
AEs	RR 1.74 (0.72 to 4.18)	436 (4 studies)	⊕⊕⊕⊕ very low ^{a,c,h}
Leukopenia	RR 0.84 (0.49 to 1.46)	281 (2 studies)	⊕⊕⊕⊕ very low ^{a,c}
Anemia	RR 0.86 (0.29 to 2.55)	723 (4 studies)	⊕⊕⊕⊕ very low ^{a,i}
Thrombocytopenia	RR 0.79 (0.52 to 1.19)	387 (2 studies)	⊕⊕⊕⊕ very low ^{a,c}
Diarrhea	RR 1.91 (0.57 to 6.42)	708 (5 studies)	⊕⊕⊕⊕ very low ^{a,c,j}
Transaminitis	RR 1.15 (0.66 to 2.01)	633 (4 studies)	⊕⊕⊕⊕ very low ^{a,c}
Increased total bilirubin	RR 0.92 (0.39 to 2.16)	330 (3 studies)	⊕⊕⊕⊕ very low ^{a,c}
Increased creatinine	RR 0.56 (0.12 to 2.72)	324 (3 studies)	⊕⊕⊕⊕ low ^{a,c}
Bradycardia	RR 2.04 (1.33 to 3.13)	487 (2 studies)	⊕⊕⊕⊕ moderate ^k

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^a Patients, caregivers, those recording outcomes, and data analysts are lack of blinding. Therefore, we decided to downgrade the quality of evidence as risk of bias.

^b There is serious heterogeneity among the studies included in the analysis of mortality ($I^2 = 81.3\%$). Overall, we decided to downgrade by one level when considering these issues along with inconsistency.

^c 95% confidence interval around the pooled effect includes both 1) no effect and 2) appreciable benefit. Overall, we decided to downgrade the quality of evidence because of imprecision.

^d There is serious heterogeneity among the studies included in the analysis of virological clearance ($I^2 = 89.8\%$). Overall, we decided to downgrade by one level when considering these issues along with inconsistency.

^e Total number of events is less than 300. Overall, we decided to downgrade the quality of evidence because of imprecision.

^f Random sequence generation and allocation concealment are unclear. The blinding of patients, caregivers, and data analysts are unclear as well. Therefore, we decided to downgrade the quality of evidence as risk of bias.

^g There is serious heterogeneity among the studies included in the analysis of intubation and mechanical ventilation ($I^2 = 67.8\%$). Overall, we decided to downgrade by one level when considering these issues along with inconsistency.

^h There is serious heterogeneity among the studies included in the analysis of AEs ($I^2 = 71.0\%$). Overall, we decided to downgrade by one level when considering these issues along with inconsistency.

ⁱ There is serious heterogeneity among the studies included in the analysis of anemia ($I^2 = 53.3\%$). Overall, we decided to downgrade by one level when considering these issues along with inconsistency.

^j There is serious heterogeneity among the studies included in the analysis of diarrhea ($I^2 = 73.2\%$). Overall, we decided to downgrade by one level when considering these issues along with inconsistency.

^k The effect was large ($RR > 2$) in analysis of bradycardia. Therefore, we decided to upgrade the quality of evidence as large magnitude of effect.

bradycardia had a moderate quality of evidence.

4. Discussion

Upon the emergency of SARS-CoV-2, we conducted this systematic review and meta-analysis to identify the potential therapeutic options for COVID-19 based on previous studies of therapies for SARS or MERS. In the present review, we included 18 articles involving 4,941 patients. Compared with control treatment, anti-coronavirus interventions significantly reduced mortality, notably augmented clinical improvement and radiographical improvement, without significant effect on symptoms alleviation, time to become afebrile, virologic eradication, incidence of ARDS, intubation, and AEs.

4.1. Hydroxychloroquine treatment

Hydroxychloroquine had earned a reputation for potential promising role in COVID-19 [42]. Increasing number of studies had been conducted and published [28,32,37,40]. Recently, chloroquine and hydroxychloroquine were demonstrated to inhibit SARS-CoV-2 *in vitro* ($EC_{50} = 5.47\mu\text{M}$, $EC_{50} = 0.72\mu\text{M}$, respectively) [32,43]. The underlying mechanisms were inferred as follows: (1) as weakly alkaline, chloroquine could increase endosomal pH therefore block virus infection [42,44]; (2) as spike (S) protein angiotensin-converting enzyme 2 (ACE2) blocker, chloroquine and hydroxychloroquine interfered with the glycosylation of cellular SARS-CoV receptor thus inhibit virus attacking [4]; (3) as immunomodulant, chloroquine and hydroxychloroquine could counteract pro-inflammatory cytokine storm in critically ill patients with COVID-19 [28,45]. Unfortunately, the outcomes of hydroxychloroquine in COVID-19 patients were inconsistent in SARS-CoV-2 viral eradication. Gautret et al reported that hydroxychloroquine alone or combined with azithromycin observed better ability of SARS-CoV-2 eradication. At day six post-treatment, 100% of patients treated with combination of hydroxychloroquine and azithromycin had been virologically cured compared to 57.1% in patients treated with hydroxychloroquine alone and 12.5% in control group [32]. On the contrary, Chen et al and Tang et al documented that the SARS-CoV-2 eradication rate were equal between hydroxychloroquine and standard care group [37,40]. Therefore, the meta-analysis generated no significant favored outcomes of hydroxychloroquine in virological eradication. The authors speculated the reasons underlying these inconsistent results included (1) unsuitable population selection: mild illness or later stage of COVID-19 might not be target population to assess the effectiveness of hydroxychloroquine; (2) inappropriate endpoints: viral load shedding rather than ICU admission and negative rate of nucleic acid might be more sensitive endpoints; (3) confounding effects: antiviral agents used in standard care group might be confounders to weaken effect of hydroxychloroquine; (4) small sample size of these studies; (5) no valid *in vivo* evidences despite adequate encouraging *in vitro* proofs [37,40]. Additionally, the hydroxychloroquine therapy improved more radiographical benefit [28], despite accompanied with more AEs especially diarrhea [40]. Up to date, we could not recommend hydroxychloroquine superior to the standard care of SARS-CoV-2 infection, and we need to wait for larger randomized trials with target population and sensitive endpoints to valid the value of hydroxychloroquine for COVID-19.

4.2. Lopinavir/ritonavir-based treatment

As an inhibitor of human immunodeficiency virus (HIV) protease, lopinavir/ritonavir was a major focus as it was recommended for patients with MERS [27] or COVID-19 [46]. It was reported lopinavir

could inhibit SARS-CoV and MERS-CoV replication *in vitro* with EC_{50} at 17.1 μM and 8 μM respectively [47]. Lopinavir was also found to demonstrated antiviral effect against SARS-CoV-2 in Vero E6 cells with EC_{50} at 26.1 μM [48]. Ritonavir had no effect against coronavirus but prolonged bioavailability of lopinavir by inhibiting host's cytochrome P450 3A4 enzyme [49]. Five studies had reported the effectiveness and safety of lopinavir/ritonavir alone or combination therapy. Lopinavir/ritonavir alone or in combination with ribavirin and corticosteroids did not show any mortality benefit. However, lopinavir/ritonavir-based treatments had observed inconsistent results of virological clearance with RR of between 0.97-2.93. Lopinavir/ritonavir alone was revealed ineffective in lowering virus load of SARS-CoV-2 [36,38], while the lopinavir/ritonavir accompanying with arbidol or ribavirin augmented the eradication of SARS-CoV-2 [27,35,47-49]. It was speculated that lopinavir/ritonavir (400 mg/100 mg) twice daily may reach the minimal lopinavir serum concentration at 9.4 μM (7.2-12.1 μM), which was inadequate for inhibition of SARS-CoV-2 [50]. Nevertheless, lopinavir/ritonavir accompanied with the other agents showing effects against SARS-CoV-2 might decrease the inhibitory concentration of lopinavir and produce synergy [48]. Furthermore, lopinavir/ritonavir-based therapies documented notably better clinical and radiographical improvement and reduced incidence of ARDS or intubation. Take adverse reactions into consideration, most of the AEs rate were comparable between groups. Conversely, lopinavir/ritonavir alone showed tendency of more diarrhea events, while the combination of lopinavir/ritonavir, ribavirin and corticosteroids reduced incidence of diarrhea significantly. It was suspected that lopinavir/ritonavir alone did not show demonstrably beneficial effects for COVID-19, but the lopinavir/ritonavir combinations might play roles in the eradication of SARS-CoV-2 [21].

4.3. Ribavirin-based treatment

The most extensively used therapies were ribavirin and ribavirin-based combinations. Ribavirin was reported to tightly bind to SARS-CoV-2 ribonucleic acid (RNA) dependent RNA Polymerase (RdRp) with binding energy of -7.8 kcal/mol, and thus may be used to against COVID-19 [51]. There were 9 studies reporting SARS and MERS patients treated with ribavirin or combinations with ribavirin. The meta-analysis yielded inconsistent results for mortality with RR of between 0.38 and 0.82, while the combination of ribavirin and corticosteroids showed remarkable lower mortality compared with control group. In addition, patients treated with ribavirin-based therapies showed comparable rates of intubation and mechanical ventilation with control group. Of note, the major problem of ribavirin was significantly higher incidence of adverse events especially bradycardia, anemia and transaminitis compared with control group. Intriguingly, the combination of ribavirin and interferon did not observe these problems. Summarily, as the inconsistent benefit, considerable safety concerns, and very low quality of evidence, it was hard to make a clear recommendation for the use of ribavirin and ribavirin-based combinations for COVID-19.

4.4. Other treatment

It was revealed that arbidol had *in vitro* antiviral activity in early replication stage of SARS-CoV [52]. However, the arbidol alone generated equivalent outcome in patients with COVID-19 compared with control group, while the addition of lopinavir/ritonavir showed better efficacy [27]. Furthermore, interferon had been widely used through SARS and MERS epidemic [18], and there were 5 studies reported

combinations with interferon. Unfortunately, no difference was noted between treatment and control group in terms of mortality, intubation rate, and adverse reactions. The recommendation of these treatments was uncertain because of the small sample size of study and other risk of low quality [12,27,36].

4.5. Strengths and limitations

Firstly, to best of our knowledge, this is the first systematic review and meta-analysis comprehensively summarized all available evidences from RCTs and cohort studies for SARS, MERS and COVID-19. Secondly, it objectively and rigorously assessed the efficacy outcomes (mortality, virological eradication, clinical improvements, etc.) and safety outcomes (AEs, leukopenia, anemia, diarrhea, bradycardia, etc.) of current anti-coronavirus therapies for SARS-CoV, MERS-CoV, SARS-CoV-2 infected patients with similar definitions of outcomes across studies. Moreover, we evaluated the quality of the evidence in the meta-analyses by implementing the GRADEpro in attempt to verify the strength of the recommendation.

On the other hand, there were some limitations among included literatures. First of all, some outcomes included a small sample size of patients, such as clinical improvement, radiographical improvement, and leukopenia, causing imprecision of outcomes thus downgraded the quality of evidence. Secondly, the open-label design of most RCTs included in this meta-analysis also restricted the quality grade of effects. Thirdly, the variations in timing of treatment, dosage, administration route and co-treatments might influence our results. For an instance, one study administrated hydroxychloroquine approximately 16 days after symptoms onset, while the time between onset of symptoms and inclusion (hydroxychloroquine initiation) were 0 to 10 days in another study. The virological eradication results were quite difference between these two studies. However, we could not perform further subgroup analysis considering these influenced factors because of the limited number of studies. Finally, the diversity of indications might add heterogeneity to results. Although SARS-CoV and MERS-CoV were closely related with SARS-CoV, the results might not be directly extrapolated to SARS-CoV-2 infected patients. Thus, further research would be required to confirm our findings.

Given the latter strengths and limitations, although we could not draw a clear conclusion for the recommendation of potential therapies for COVID-19 considering the very low quality of evidence and wide heterogeneity of interventions and indications, our results may help clinicians to comprehensively understand the advantages and drawbacks of each anti-coronavirus agents on efficacy and safety profiles. Lopinavir/ritonavir combinations might observe better virological eradication capability than other anti-coronavirus agents. Conversely, ribavirin might cause more safety concern especially bradycardia.

4.6. Suggestions for future clinical trial

Currently, growing trials related to anti-coronavirus agents were ongoing, including 18 for hydroxychloroquine, 13 for chloroquine, 7 for remdesivir, 6 for lopinavir/ritonavir, 5 for interferon, 3 for favipiravir, 2 for arbidol, and 13 for combinations. The detailed information of registered trials is shown in Supplementary Table 4. These ongoing studies would facilitate our understanding of the optimal anti-coronavirus approach for COVID-19 patients. Based on previous observations, we provided some proposal and suggestions for further clinical trials as follows: (1) larger-scaled RCTs were utmost needed; (2) severe COVID-19 patients rather than mild or moderate patients should be favored investigated population; (3) confounders such as anti-viral agents used in control group should be adjusted or balanced; (4) the dosage and initial time of regimens should be standardized, for instance, the anti-coronavirus agents should be used at early stage of illness; (5) specific endpoints such as mortality, virological eradication or viral loading shedding, and clinical outcomes (including symptoms

improvement, radiographical results improvement, intubation rate and ICU admission) should be estimated.

5. Conclusions

There was evidence of lower mortality, better clinical and radiographical improvement in intervention group compared with control group. In subgroup analysis, ribavirin combined with corticosteroids, lopinavir/ritonavir-based therapies and hydroxychloroquine showed some benefit in different outcomes. However, considering the very low quality of evidence, the heterogeneity of interventions and indications, we could not draw a clear conclusion for the recommendation of potential therapies for COVID-19. Our results may allow clinicians to comprehensively understand the property of each anti-coronavirus agent on efficacy and safety outcomes and thus may constitute a basis of drug treatment for COVID-19. Certainly, it was of utmost necessity to conduct large-scale clinical trials to objectively assess the efficacy of antiviral treatment on the mortality, virological and clinical outcomes of SARS-CoV-2 infections.

Contributions

Zhi-Chun Gu was responsible for the study design. Yue-Tian Yu, Yuan Gao, and Hou-Wen Lin provided administrative management. Zai-Li Zhang and Han Zhong conducted the searching and screening of literatures. Subsequently, the data was extracted and analyzed by Han Zhong and Zai-Li Zhang. Moreover, Han Zhong, Yan Wang, Zai-Li Zhang and Zhi-Chun Gu were contributed to the manuscript writing. Finally, all authors approved the full manuscript.

Ethical Statement

Ethical approval is not necessary because the present study is a systematic review and meta-analysis. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

None conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.phrs.2020.104872>.

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